February 5, 2003

Randy Deskin, Ph.D.
Director, Toxicology and Product
Regulatory Compliance Department
Cytec Industries, Inc.
5 Garret Mountain Plaza
West Paterson, NJ 07424

Dear Dr. Deskin:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for m-phenylenediisopropylideneisocyanic acid posted on the ChemRTK HPV Challenge Program Web site on October 10, 2002. I commend Cytec Industries, Inc. for their commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Cytec advise the Agency, within 60 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
A. Abramson
W. Penberthy
M. E. Weber

EPA COMMENTS ON CHEMICAL RTK HPV CHALLENGE SUBMISSION: m-Phenylenediisopropylideneisocyanic Acid

SUMMARY OF EPA COMMENTS

The sponsor, Cytec Industries Inc., submitted a test plan and robust summaries to EPA for *m*-phenylenediisopropylideneisocyanic acid (tetramethyl-m-xylylene diisocyanate (TMXDI, CAS No. 2778-42-9) dated September 19, 2002. EPA posted the submission on the ChemRTK HPV Challenge web site on October 10, 2002.

EPA has reviewed this submission and reached the following conclusions:

1. Physicochemical Properties and Environmental Fate. The data provided by the submitter for
most endpoints are adequate for the purposes of the HPV Challenge Program. The submitter needs to address data adequacy issues for stability in water and water solubility.

2. Health Effects. The data are adequate for all SIDS endpoints except chromosomal aberrations and reproductive/developmental toxicity. EPA agrees with the submitter's plan to conduct chromosomal aberration and developmental toxicity testing. The submitter also needs to specify the guidelines to be followed, provide a robust summary for the relevant reproductive effects data, and address deficiencies in the robust summaries.

3. Ecological Effects. EPA reserves judgment on the adequacy of the data for fish and invertebrates until the submitter provides information on the quantity of acetone used in key studies. The algal data are adequate, but the submitter needs to address a few deficiencies in the robust summaries.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON THE m-PHENYLENEDIISOPROPYLIDENEISOCYANIC ACID

CHALLENGE SUBMISSION

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data provided by the submitter for melting point, boiling point, vapor pressure, and octanol/water partition coefficient are adequate for the purposes of the HPV Challenge Program.

Water solubility. The submitter provided a water solubility value of 5.833 mg/L , estimated using WSKOW (v. 1.40). According to OECD guidelines, water solubility values need to be measured if the estimated values are $1 µg/L (1ppb); qualitative descriptions (e.g. very soluble, insoluble) are not acceptable. If this chemical hydrolyzes slowly, as the submitter states, then its water solubility should be measured following OECD Guideline 105. However, if it is found to hydrolyze rapidly (like most isocyanates) then the estimated water solubility will be adequate, as water solubility measurements may not be attainable.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data provided by the submitter for photodegradation and biodegradation are adequate for the purposes of the HPV Challenge Program.

Stability in water. The submitter estimated the hydrolysis of this chemical using HYDROWIN (v1.67) and considers the endpoint satisfied. No clear argument was presented for not conducting hydrolysis testing. The robust summary states that the material will react slowly with water to form insoluble ureas. However, isocyanates generally hydrolyze very rapidly. A HYDROWIN estimation (EPIWIN v 3.10) by EPA indicates that even at low pH the hydrolysis rate is very fast ($t_{1/2}$ <10 minutes). The submitter needs to measure this endpoint following OECD Guideline 111. As indicated under *Water solubility* if this compound does hydrolyze slowly then its water solubility needs to be determined experimentally.

Transport and distribution (fugacity). The data provided by the submitter for transport and distribution (fugacity) are adequate for the purposes of the HPV Challenge Program. All the submitter's estimates have assumed that chemical hydrolysis is slow; however, as most isocyanates hydrolyze rapidly, the submitter will need to rerun the model if a measured hydrolysis value is obtained.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, reproductive/developmental toxicity)

Adequate data are available for acute toxicity, repeated-dose toxicity, and gene mutation. The submitter plans to conduct tests for chromosomal aberrations and developmental toxicity but did not specify protocols. EPA recommends the OECD 473 (in vitro cytogenetic assay) and 421 (combined reproductive/developmental toxicity) Guidelines.

Reproductive toxicity. The histopathology data on male and female reproductive organs from the submitted 14-week repeated-dose inhalation study will satisfy the reproductive toxicity endpoint for the purposes of the HPV Challenge Program when combined with an adequate developmental toxicity study (which the submitter plans to perform).

Also, when a study addresses multiple endpoints, a robust summary is needed for each endpoint. Therefore, the submitter will need to provide a robust summary for reproductive effects.

Ecological Effects (fish, invertebrates, and algae)

EPA reserves judgment on the adequacy of the data for fish and invertebrates until the submitter provides information on the quantity of acetone used in key studies. The algal data are adequate, but the submitter needs to address a few deficiencies in the robust summaries.

Specific Comments on the Robust Summaries

Environmental Fate

Transport and distribution (fugacity). The robust summary needs to include the values of the model input parameters. The submitter needs to rerun the model if measured hydrolysis values become available.

Health Effects

Although the five robust summaries reviewed provide sufficient information to evaluate the studies, most are incomplete.

In addition, the submitter needs to address two flaws in overall data presentation: (1) exposure concentration units in the acute and repeated-dose inhalation studies should be the same; (2) LOAEL values should be reported for both repeated-dose inhalation studies (especially the 90-day assay, since a NOAEL was not established).

Acute Toxicity. Two robust summaries were provided. For a rat acute oral toxicity study, omissions included mortality and body weight data by dose and sex, the extent of body weight changes, and the method used to calculate the LD_{50}. For a 4-hour rat inhalation

toxicity study, omissions included the extent of body weight changes by exposure level and sex.

Repeated-Dose Toxicity. Two robust summaries were provided, and common omissions included organs selected for weighing and histopathological examination, all hematology and serum chemistry parameters measured (only values with significant changes were reported), and the extent of body weight changes. The 4-week study summary also omitted the particle size distribution of the test aerosol and did not identify NOAEL or LOAEL values. The 14-week study summary omitted measured urinalysis parameters and the incidence of mortality and nasal lesions by exposure level and sex. The submitter states on page 50 that there were no mortalities in the 14-week study. However, on page 51 a number of mortalities were identified. The submitter needs to address this discrepancy, and, if mortalities did occur, list the dose and time of death.

Genetic Toxicity. A robust summary for a negative mutagenicity assay in *Salmonella typhimurium* omitted the purity of the test material.

Ecological Effects

Fish. For the 96-hour test with *Pimephales promelas*, the amount of solvent (acetone) used was not given. This information is needed to determine the adequacy of the test data. Also, water chemistry parameters apparently were measured, but the values were not reported. The submitter needs to provide this information in the robust summary.

For the 96-hour test in *Lepomis macrochirus*, the submitter needs to provide information on test substance purity, water chemistry measurements, and analytical monitoring details. In addition, the Results section states that the NOEC and LC_{50} values were "based on WAF exposure, measured by analysis," but the Summary Details section states that "all results were based on nominal concentrations." The submitter needs to address this inconsistency.

Invertebrates. The submitter needs to provide information on the amount of solvent (acetone) used.

Algae. The submitter needs to provide information on test substance purity and test temperatures.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.